INFLUENCE OF TISSUE SPECIFIC MACROMOLECULE BASELINE ON THE METABOLITE QUANTIFICATION IN HUMAN BRAIN AT 7 TESLA

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Introduction: Localized ^{1}H spectroscopy allows non-invasive acquisition of NMR spectra and provides direct insight into brain metabolism. At short echo time (TE), metabolite resonances are better resolved and ^{1}H spectrum exhibits a broad underlying signal coming from the macromolecules (MM). Variations of the MM shape, due to local brain structure in healthy subjects have been previously reported at 1.5T [1]. At 3T and lower field, MM can be approximated by a set of mathematical functions but, at higher fields, the improved spectral resolution [2] requires the acquisition of the *in-vivo* MM signal for an accurate quantification of the metabolites. Inaccuracy in the measurement of the MM might lead to systematic errors or even prevent simulation of sharp metabolite resonances. Tissue differences of MM in human brain have not been studied at high field, thus to further understand their neurochemical profile and their intrinsic properties, they have been acquired with the semi-adiabatic SPECIAL (SPin Echo full Intensity Acquired Localized Sequence) [3], preceded by an inversion pulse, in two different tissues (white matter and grey matter). The aim of this study is to compare MM baselines acquired in two different tissues (WM and GM) and to evaluate the potential differences on the LCModel (S. Provencher Inc, USA) quantification of the metabolites.

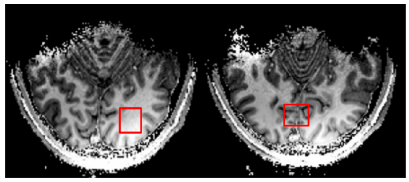

Fig. 1: *Location of the voxel (red) for the acquisition (VOI=20×15×20mm^3) of the WM (left) and GM (right) MM baseline.*

Materials and Methods: Ten healthy subjects (8 men, 2 women aged 20 to 28 years) gave informed consent according to the procedure approved by the local ethics committee. A home-built shielded quadrature transmit/receive surface RF coil (R=6cm) was used to measure spectra in a 7T Siemens scanner. Two locations in the occipital lobe were investigated, predominantly grey matter (GM) or white matter (WM), using five subjects for each (fig 1). MP2RAGE [4] was first performed to determine the composition of the voxel of interest by segmentation of 3D images in terms of WM, GM and cerebral-spinal fluid. First and second order shims were adjusted using FASTMAP [5]. MM spectra were acquired in the aforementioned locations using the IR semi-adiabatic SPECIAL sequence (TR/TI/TE=7500/950/12ms, BW=4000Hz, vector size=2048pts, 32×2 scans, VOI=20×15×20mm^3) employing VAPOR water and outer volume suppression [6]. The residual metabolite spectrum was obtained using the same sequence parameters except of a long-TE (TE=30ms, 16×2 scans). *In vivo* ^{1}H spectrum were acquired with the standard semi-adiabatic SPECIAL (TR/TE=7500/12ms, 16×2 scans, no inversion). The individual ^{1}H MR spectra were frequency and phase corrected before averaging, using Matlab. Correction of the MM spectrum was performed with jMRUI using AMARES by fixing the linewidth, the frequency, the phase and the amplitude of the Lorentzian functions. Metabolites were quantified using LCModel with a basis set of simulated spectra of 21 metabolites and the corrected macromolecule baseline (WM or GM). A concentration of Creatine of 8.5µmol/g was used as an internal reference. Statistical test were based on a paired ANOVA, for testing the relevance of the choice of a local baseline on the quantification.

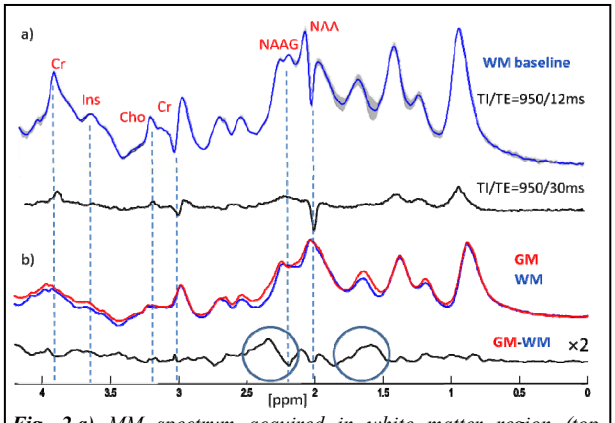

Fig. 2.a) *MM spectrum acquired in white matter region (top, 64scans, n=5) with metabolite residual clearly identified at long-TE (bottom, 32 scans). MM spectrum is presented as the mean (blue) ± s.d. (shadow).**2.b)** Top: Corrected MM baselines acquired in GM (red) and WM (blue) region. Bottom: Difference spectrum between GM and WM (bottom) exhibits differences in the regions encircled.*

Results and Discussion: Shimming resulted in typical water linewidths of 12-13.5 Hz. The location of the voxel and the placement of OVS bands were carefully set to minimize lipid contamination. ^{1}H spectra with lipid contamination were discarded. The mean content of WM and GM in their respective voxel was 60±2% and 75±5% (mean±s.d., n=5). The experiment is highly reproducible and the acquired MM baselines seemed fairly constant between the healthy subjects (small standard deviation, scale to MM01 at 0.91ppm, fig. 2.a top). An optimum inversion time was set to 950ms, leading to a MM spectrum with the smallest metabolite residuals. The latter were identified at long-TE (fig. 2.a bottom) and due to the long T_1. Information on metabolite concentration and their T_1 values could be extracted from the MM spectra. For instance, the short T_1 and the higher concentration of NAAG in WM compare to GM [7] generated a peak at 2.2ppm in WM (fig. 2.b) but not GM baseline. Once residuals were assigned to specific metabolites, a correction was applied with jMRUI using AMARES with a set of Lorentzian functions. The comparison between the corrected MM baselines (fig. 2.b) revealed a slight variability in the shape with a higher concentration of macromolecules for GM in the region 1.5-1.6ppm and 2.3-2.6ppm. The MM baselines were then inserted into the basis sets of LCModel to quantify the ^{1}H NMR spectra. Depending on the choice of the baseline (WM or GM), small (within the standard deviation) but significant ($p<0.001$) differences were detected in the metabolite quantification (fig. 3) for Glu, Gln, NAA (<10%) and Asp (<20%) revealing that the macromolecule signal difference between WM and GM at 2.3-2.6ppm has a direct influence on the quantification of the metabolites. These observed tissue MM differences (fig. 2.b) are in agreement with the previous study at 1.5T [1].

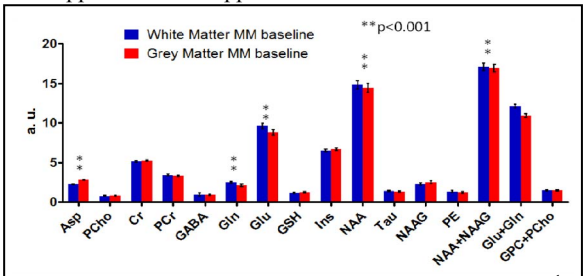

Fig. 3: *Metabolite concentration (mean±sem., n=5) of ^{1}H spectra acquired in white matter region using the MM baseline measured in white matter (red) or grey matter blue). Significant changes are obersved for Gln, Glu, NAA, Asp.*

Based on this preliminary experiment and given the small observed changes on the quantification, we conclude that a general *in vivo* measured MM baseline seems sufficient to ensure a reliable quantification of the metabolites in the human brain at 7T.

References and Acknowledgements: [1] Hofmann *et al.*, 2001 [2] R. Gruetter *et al.*, JMR, 2007 [3] V. Mlynarik *et al.*, MRM, 2006 [4] Marques JP *et al.*, Neuroimage, 2010 [5] R. Gruetter et al., MRM, 1993 [6] I. Tkac *et al,* AMR, 2005 [7] P.J.W. Pouwels *et al.*, NMR in BioMed. 10:73-78, 1997. Supported by CIBM of the UNIL, UNIGE, HUG, CHUV, EPFL, the Leenaards and Jeantet Foundations and SNF grant 131087.